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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/169,289 09/29/98 DIETZ H 07265/098002

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EXAMINER

SCHMIDT.M

ART UNIT

PAPER NUMBER

1635

4

DATE MAILED:

02/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/163,287

Applicant(s)

Dietz

Examiner

Schmidt

Group Art Unit

1635

--The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address--

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

Responsive to communication(s) filed on _____

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-11 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

☒ Claim(s) 1-11 is/are rejected.

Claim(s) _____ is/are objected to.

Claim(s) _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The proposed drawing correction, filed on _____ is approved disapproved.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 2

Interview Summary, PTO-413

☒ Notice of References Cited, PTO-892

Notice of Informal Patent Application, PTO-152

Notice of Draftsperson's Patent Drawing Review, PTO-948

Other _____

Office Action Summary

Art Unit: 1635

DETAILED ACTION

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,814,500. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims broadly encompass all the limitations of the claims of '500.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

Art Unit: 1635

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the scope of the invention as claimed in U.S. Patent 5,814,500, does not reasonably provide enablement for the breadth of nucleic acid constructs and methods instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claim 1 is drawn to any nucleic acid construct for suppressing gene expression comprising a 5' stem loop structure, an antisense nucleic acid and a 3' stem loop structure. The claim broadly reads on a broad scope of possible antisense or ribozyme structures. Further, claims 13 and 15 read on administration of such nucleic acid constructs to any cell, including a cell in a whole organism. These claims therefore read on gene therapeutic applications of the claimed nucleic acid constructs.

The specification as filed teaches by way of example several antisense constructs flanked by 5' and 3' U1 snRNA stem loop structures for expression in cells in cell culture. The specification as filed does not provide any examples of administration of such constructs to whole organisms.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach

Art Unit: 1635

the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunately, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture

Art Unit: 1635

inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed.

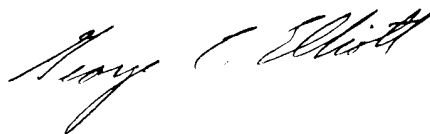
The quantity of experimentation required to make and use the invention as claimed would include (1) identification of a broad scope of possible nucleic acid constructs having stem loop structures, (2) testing said structures for functional antisense activity both in cell culture and (3) development of pharmaceutical formulations for expression in whole organisms. Therefore, it would require undue experimentation to practice the invention as claimed in view of the lack of guidance in the specification as filed and the unpredictability in the art for such factors.

Art Unit: 1635

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A handwritten signature in cursive script, appearing to read "Mary M. Schmidt".

M. M. Schmidt
January 30, 2000